General

Guideline Title

ACR Appropriateness Criteria® locally advanced breast cancer.

Bibliographic Source(s)

MacDonald SM, Haffty BG, Harris EE, Arthur DW, Bailey L, Bellon JR, Carey L, Goyal S, Halyard MY, Horst KC, Moran MS, Expert Panel on Radiation Oncology--Breast. ACR Appropriateness CriteriaÂ® locally advanced breast cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 13 p. [119 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Strom EA, Yu T, Rabinovitch RA, Haffty BG, Halberg FE, Taylor ME, White JR, Cobleigh MA, Edge SB, Expert Panel on Radiation Oncology-Breast. ACR Appropriateness Criteria® locally advanced breast cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 12 p.

The appropriateness criteria are reviewed biennially and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Locally Advanced Breast Cancer

Variant 1: 57-year-old woman, triple negative IDC, status post-mastectomy: 3.5 cm inner quadrant primary, 7/12 LN (+). Focally positive deep margin. PET (+) IMN and supraclavicular nodes. Adjuvant anthracycline and taxane, with normalization of PET findings. Metastatic workup negative.

Treatment	Rating	Comments
Radiation Volumes		
Chest wall only ± boost	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
Supraclavicular + apical nodes (assumes chest wall RT also)	9	
Full axilla (assumes chest wall RT also)	7	
Internal mammary nodes (assumes chest wall RT)	9	
Boost to IMC	8	
Boost supraclavicular nodes	8	
Radiation Doses		
Total dose to chest wall including boost: 45-50 Gy	1	
Total dose to chest wall including boost: 60 Gy	2	
Total dose to chest wall including boost: 64-66 Gy	9	Clinical circumstance may require higher dose.
Total dose to supraclavicular fossa including boost: 45-50 Gy	9	
Total dose to supraclavicular fossa including boost: 60-66 Gy	9	
Total dose to entire IMN chain: 45-50 Gy	9	
Total dose to entire IMN chain: 60-66 Gy	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 2: 55-year-old woman with neglected primary. Large, fungating lesion and matted axilla. ER (–)/PR (+), Her2 (–). Metastatic workup negative. Not operable after three chemo regimens, including anthracyclines and taxanes.

Treatment	Rating	Comments
Principles of Treatment		
Switch to endocrine therapy	9	
Preoperative RT (50-54 Gy)	8	
Concurrent chemoradiation	6	May be appropriate in selected clinical circumstances.
Definitive RT ≥ 70 Gy	4	May be appropriate in selected clinical circumstances and if no other options are available. Risk of brachial plexopathy increases if this
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments dose is delivered to supraclavicular region.
Switch to 4th line chemotherapy	3	Appropriate in phase I clinical trial.
Debulking surgery with anticipated + margins	3	
Palliative radiation (30-45 Gy)	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 3: 40-year-old woman, 4 cm primary with diffuse suspicious microcalcifications in breast, direct skin invasion, satellite skin nodule, matted axilla (N2), ER (+)/PR (–), Her2 (–). Metastatic workup negative.

Treatment	Rating	Comments
Principles of Treatment		
Initial chemotherapy	9	
Mastectomy if response to initial chemotherapy	9	
Initial endocrine therapy	2	Only if cytotoxic therapy is contraindicated or on a clinical trial.
Initial surgery	1	
Initial breast and nodal RT	1	
BCT if response to initial chemotherapy	1	
Radiation Volumes (assume chemotherapy, mastectomy, axillary dissection level I-II, 3/16 LN+)		
Chest wall only ± boost (no nodal RT)	1	
Chest wall, supraclavicular and apical nodes	9	
Chest wall, supraclavicular fossa + full axilla	7	
Internal mammary nodes (assumes chest wall RT)	8	
Boost to chest wall	7	
Radiation Doses (1.8–2.0 Gy/day unless specified otherwise) (assume chemotherapy, mastectomy, clear margins, and axilla dissection level I-II, 3/16 LN+)		
Chest wall: 45-50 Gy	9	
Boost to chest wall: 60-66 Gy	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
Supraclavicular and axillary nodes: 45-50 Gy	9	
Full axilla: 45-50 Gy	7	
IMN: 45-50 Gy	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 4: 80-year-old woman, 4 cm primary, direct skin invasion, satellite nodule, matted axilla (N2), strongly ER/PR (+), Her2 (–). Metastatic workup negative. Medically fit.

Treatment	Rating	Comments
Treatment Modalities		
Initial endocrine therapy	9	Both initial endocrine therapy and initial chemotherapy are considered equally appropriate.
Initial chemotherapy	9	Both initial endocrine therapy and initial chemotherapy are considered equally appropriate.
Initial surgery	1	
Initial breast and nodal RT	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 5: 45-year-old premenopausal woman, 4.5 cm IDC left breast, ER/PR (-), Her2 amplified, PET (+) in breast, axilla and medial infraclavicular fossa. Palpable nodes in high axilla. Metastatic workup negative. Patient desires breast conservation.

Treatment	Rating	Comments
Principles of Treatment		
Initial chemotherapy plus Her2-directed therapy	9	
Breast conservation therapy (BCT) if ≥partial response (PR) to chemotherapy	8	For some patients with less than a partial response, breast conservation may be appropriate if surgically feasible.
Initial mastectomy and axillary dissection	1	N3 status contraindicates initial surgical approach.
Initial BCT and axillary dissection	1	
Radiation Volumes (assume initial chemotherapy followed by BCT, clear margins, and axilla dissection level I-II, 8/16 LN+, highest node+)		
Whole breast only ± boost (no nodal RT)	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
Partial breast irradiation (no nodal RT)	1	
Whole breast and supraclavicular + apical axillary nodes	9	
Whole breast and supraclavicular LNs and full axilla	7	Probably not required after a standard axillary dissection.
Internal mammary nodes (assumes breast RT given concurrently)	8	Provided caution is taken to minimize cardiac pulmonary volumes.
Boost infraclavicular region	8	Boost determined by extent of surgical resection and clinical features.
Radiation Doses (1.8-2.0 Gy/day unless specified otherwise) (assume initial chemotherapy followed by BCT, clear margins, and axilla dissection level I-II, 8/16 LN+, highest node+)		
Whole breast: 42.5 Gy (16 fractions)	1	Despite available data for early-stage disease, little data exist for this fractionation scheme in the setting of chemotherapy and postneoadjuvant treatment.
Whole breast: 45-50 Gy	9	
Total dose to breast tumor bed: 45-50 Gy	1	
Total dose to breast tumor bed: 60-66 Gy	9	
Total dose to supraclavicular fossa and axillary apex: 45-50 Gy	9	
Total dose to supraclavicular fossa and axillary apex: 60 Gy	1	
Total dose to medial infraclavicular nodes: ≥60 Gy	8	Gross tumor may require higher doses. Higher doses risk brachial plexus. CT planning recommended.
Full axilla: 45-50 Gy	7	
IMN: 45-50 Gy	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 6: 38-year-old woman, T4 inflammatory, N1 disease, no response post 3-cycle multidrug chemotherapy. ER/PR (–), Her2 (–). Metastatic workup negative.

Treatment	Rating	Comments
Principles of Treatment		
Change chemotherapy; if no response progressive disease, proceed to RT	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
Change chemotherapy; if response, mastectomy		
Change chemotherapy; if no response, pre-op chemoradiation (radiosensitizing chemotherapy)	7	
Immediate mastectomy/axillary dissection	1	
Radiotherapy (assume sufficient response to be operable with clear margins)		
Standard fractionation (1.8-2.0 Gy)	9	
Accelerated fractionation (1.5 Gy BID)	7	
Dose to central chest wall: 45-50 Gy	9	
Total dose to chest wall including boost: 60-66 Gy	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 7: 50-year-old woman, T3N2M0 disease, with clinical CR post 4-cycle multidrug chemotherapy. ER/PR (–), Her2 (–). Does not desire BCT.

Treatment	Rating	Comments
Treatment Modalities		
Mastectomy and axillary dissection	9	
Additional chemotherapy	9	Would complete all chemotherapy up front. Depends on what drugs are used.
Postmastectomy RT	9	
No surgery: RT + chemotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 8: 42-year-old woman, T2N1 (clinical), M0 left breast cancer, Her2 amplified. Status post mastectomy with 11/12 (+) nodes and reconstruction plus chemotherapy, no evidence of disease. Margins negative. Will receive trastuzumab for 1 year.

Treatment	Rating	Comments
Principles of Treatment		
Chest wall RT	9	Try to exclude all heart from RT volume
Supraclavicular RT	9	Try to exclude all heart from RT volume

Treatment	Rating	Comments
Total RT dose delivery of 50 Gy or 50.4 Gy without boost	8	Reasonable to deliver radiation at 1.8 Gy per fraction. Because the delivery of a boost is considered controversial, it is very reasonable to omit the boost in this clinical situation.
Full axilla RT	8	
IMN RT	8	
Discontinue trastuzumab during radiotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

The treatment of locally advanced breast cancer (LABC) must include two major goals: control of locoregional disease and eradication of occult systemic metastases. The patterns and risk of locoregional recurrence after mastectomy are functions of the size of the primary tumor, the degree of regional nodal involvement, the presence or absence of skin or chest wall involvement, and the type of surgical procedure performed.

In this document, LABC includes bulky primary breast tumors (large tumors or those involving the skin or chest wall) and breast cancers with extensive lymphadenopathy, as defined by the American Joint Committee on Cancer (AJCC) staging system. LABC includes clinical T3, T4, N2, or N3 disease. Patients with LABC have historically had a poor prognosis, and some are initially inoperable. They include patients with evidence of multiple (≥4) or matted axillary lymph nodes or involvement of the second-echelon nodal basins of the infraclavicular, supraclavicular, and internal mammary lymph nodes (IMN). A clinically distinct but similarly high-risk type of LABC is inflammatory breast cancer. Overall, LABC is very heterogeneous, with highly variable tumor sizes and nodal status. This definition was chosen in a way to integrate with the ACR Appropriateness Criteria® topics on Local Regional Recurrence and Salvage Surgery — Breast Cancer and Postmastectomy Radiotherapy. The discussion for this topic is limited to avoid significant overlap with the other two topics.

Breast imaging is important to determine the extent of primary disease and to evaluate for multifocal, multicentric, or contralateral breast cancer. A bilateral diagnostic mammogram with compression or magnifications views if needed is essential for all breast cancer patients. Ultrasound (US) may provide additional information regarding breast malignancy and may also be used to evaluate the axilla. US-guided biopsy may be performed for enlarged lymph nodes or lymph nodes demonstrating architectural distortion. The sensitivity of US is low, and therefore patients with negative axillary lymph nodes by US will still require surgical evaluation with sentinel lymph node biopsy or axillary lymph node dissection. Magnetic resonance imaging (MRI) has been increasingly used and recognized as an important tool in evaluating the extent of disease for LABC. It is useful for detecting abnormal lymph nodes and contralateral disease, and it may aid in determining if a mastectomy is feasible without neoadjuvant therapy. MRI can also be used for evaluating response to neoadjuvant chemotherapy. Because of the high probability of metastatic disease in patients with LABC, imaging studies including bone scan and computed tomography (CT) of the upper abdomen and chest are useful. Positron emission tomography (PET) is sometimes used in lieu of CT of the chest and abdomen, and sometimes bone scan, although there is not universal agreement on which of these modalities may be preferred.

A study reporting the outcome of untreated patients diagnosed with breast cancer found a median survival time of 2.7 years. The median 5-year overall survival (OS) rate was 18%, and the median 10-year OS rate was 4%. Local therapy improved on these numbers in many cases, even in patients with advanced breast cancer. After another study showed no benefit with radical mastectomy in patients with skin ulceration, skin edema (peau d'orange) or erythema, satellite skin nodules, or fixation to the chest wall musculature, only patients with operable disease were treated by mastectomy, with or without radiotherapy, while inoperable disease was treated by radiotherapy alone. Most of the patients succumbed due to distant metastases. However, there were still 20% to 50% 5-year survivors when the patients were treated using definitive radiation with various systemic adjuvant chemotherapies. The local control in these patients ranged from 50% to 70%.

For operable patients undergoing mastectomy without irradiation, certain subgroups at higher risk for recurrence were identified. The clinical and pathologic status of axillary nodes was found to be an important indicator of the risk of both subsequent local recurrence (LR) and distant metastasis (DM). Patients having four or more nodes involved at mastectomy had locoregional recurrence rates (LRR) of 22% to 38% and were at significant risk of locoregional recurrence regardless of the primary tumor size. An increasing number of involved lymph nodes are a powerful predictor of locoregional recurrence and metastasis.

In attempts to improve survival and local-regional control (LRC), adjuvant radiation was initially added to definitive surgeries. With this combination of therapies, one group of researchers reported a 10-year LRC of 82% and a 10-year disease-specific, recurrence-free survival rate (DSRFS) of 40%. Even after adjuvant radiation, a higher number of involved axillary lymph nodes predicted worse LRC and DSRFS. In another study, definitive surgery rather than lesser surgeries was needed, along with adjuvant radiation, to have better OS, RFS, and LRC. Initial mastectomy is not indicated in patients with stage IIIB disease and should be avoided in lower stages of disease unless the tumor can be completely resected. The value of subtotal tumor excision has not been demonstrated.

Combined Modality Therapy — Mastectomy

The earliest reports of induction chemotherapy were published in the 1970s. The sequence of treatment has varied; mastectomy often precedes other therapy for operable patients, although many institutions have preferred to use preoperative systemic or radiation therapy (RT) or both. Randomized trials and the Oxford meta-analysis have shown that adjuvant systemic therapy has resulted in lower recurrence rates and increased survival.

In the most recent Oxford meta-analysis, the addition of RT also showed significant improvement in OS. However, the trials in the meta-analysis included mostly early-stage breast cancer patients. Few randomized studies have evaluated only stage III disease, and these have mostly excluded patients with inoperable disease.

Trials comparing the combination of chemotherapy with either RT or surgery as local monotherapy in patients with advanced breast cancer have reported high (25% to 30%) local recurrence rates. Retrospective studies suggested that better LRC and DFS results were obtained with trimodality therapy than with any other combination of therapies. In one study patients who received neoadjuvant chemotherapy with mastectomy alone were compared with those who also received postmastectomy RT. Over 67% of patients were stage III in the study. In multivariate analysis, adjuvant RT independently contributed to better LRC and cause-specific survival. Even when patients achieved complete pathologic response after neoadjuvant chemotherapy, there was a high rate of LRR (33% at 10 years). The addition of RT further reduced that rate to 3% at 10 years. In a small group of patients who were inoperable and resistant to anthracycline-based chemotherapy, preoperative RT was able to convert over 80% of patients to operable status and allow them to undergo mastectomy. Nearly half of these patients were alive at 5 years, with 64% local control.

In 1997, the Eastern Cooperative Oncology Group (ECOG) reported the results of its trial of postmastectomy locoregional RT in technically resectable LABC. All 312 patients received chemohormonotherapy consisting of CAFTH for 6 cycles. The patients were then randomized to adjuvant RT or delayed RT until LRR. The patients in the adjuvant RT arm had lower LRR (15% vs 24%) but higher DM rates (50% vs 35%) as first site of failure compared to patients in the delayed RT arm. The study population had high competing risk for DM. There was no difference in OS rate or time to overall relapse. Of note, 30 of 164 patients in the adjuvant RT arm did not actually receive radiation; 11 of these patients had LRR as first site of failure.

A randomized trial in stage III breast cancer patients from Helsinki has clearly shown the efficacy of combining all three therapeutic modalities of surgery, chemotherapy, and RT. In this trial, 120 patients with stage IIIA breast cancer were randomized to one of three arms after modified radical mastectomy: locoregional irradiation alone, systemic VAC (vincristine, adriamycin, cyclophosphamide) chemotherapy (with or without levamisole), or both VAC and irradiation. At both 3 and 5 years, RT reduced local failures relative to the chemotherapy arm, whereas VAC reduced the number of distant failures. The best DFS and local control rates were seen in the combined-modality arm.

In the Danish Breast Cooperative Group trials (82b and 82c), adjuvant RT improved OS in patients who underwent modified radical mastectomy and systemic chemotherapy with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) if premenopausal or with tamoxifen if postmenopausal. However, in those studies, only 12% to 14% of the studied patients had T3 primary tumors or skin invasion and unspecified patients and clinical N2 or N3 disease. Similarly, the British Columbia randomized trial that showed improved LRC and breast-cancer-specific survival with the addition of adjuvant RT to modified radical mastectomy and CMF, had very few LABCs. Therefore, interpretation of those results to LABC is difficult.

Based on the above studies as well as the other studies previously mentioned, it appears that surgery and RT produce essentially equivalent local control rates when used alone with systemic therapy, but these control rates are only in the range of 60% to 70%, whereas when they are used together, superior local control rates of 80% to 90% can be achieved. This multidisciplinary approach to LABC renders most patients local regionally disease free.

Combined-Modality Breast-Preserving Therapy

Breast preservation is feasible in certain LABC patients. Those with clinical N2/N3 disease and small primary tumors, whose nodal disease responds to neoadjuvant chemotherapy, should be offered breast-preserving therapy. Many patients with large primary tumors may also be treated with breast conservation if a good response to neoadjuvant therapy is achieved. Trials comparing preoperative and postoperative chemotherapy

have reported higher rates of breast-conserving therapy with preoperative chemotherapy, and studies suggest that up to one-quarter of patients with advanced breast cancers can be offered breast preservation. Appropriate patient selection is very important. Patients with multicentric disease or extensive calcifications are not good candidates for breast-conserving therapy following neoadjuvant treatment. All patients undergoing breast-conserving therapy should receive adjuvant whole-breast irradiation. For patients with T4 disease, breast conservation should be offered as part of the study protocol, although a small study suggested its feasibility. In the U.S., initial chemotherapy is probably the most common approach to treating inoperable LABC, with response rates an important factor in predicting local control irrespective of the type of surgery required to remove the disease. Patients with inflammatory breast cancer should not be considered candidates for breast-conserving therapy.

There have been some attempts to forgo surgery for patients who responded well to neoadjuvant chemotherapy or hormonal therapy. In one study only RT was given to those patients who achieved clinical complete response and whose breast biopsy was negative. There was a trend for worse LRC in the RT-alone group compared to those who also had mastectomy and radiation. Therefore, this strategy should still be considered investigational.

Inflammatory Breast Cancer

Inflammatory breast cancer (T4d) is seen in a small subset of patients, but is still a very aggressive disease with worse prognosis than other LABCs. Before the era of systemic chemotherapy, 5-year survival rates were in the range of only 5%. Since the use of induction chemotherapy, 5-year survival figures have risen to 30%-50%.

Trimodality therapy should be considered the standard approach for patients with inflammatory breast cancer. Several series have suggested higher local and regional failure rates when surgery is not included as a component of therapy, although the survival benefit is less clear. However, a group of researchers reported significantly improved LRC and OS rates for patients receiving surgery as part of initial treatment: LRR (19% vs 70%, $P<0.0001$) and 5-year OS (37% vs 7%, $P=0.0004$). This may have been a reflection of the favorable outcome of patients who respond to chemotherapy, because other series have shown that the initial responders will also have the best survival rates. For instance, another group of researchers reported 5-year OS of 83% in patients with pathologic complete disease remission in the axillary lymph nodes, while the same rate dropped to 37% if tumor was still detected in the lymph nodes after chemotherapy.

When combined modalities were used, high rates of LRC could be reached. One study reported 5-year LRC of 73% in patients who received chemotherapy, mastectomy, and RT. There were still high rates of DM and mortality, with OS of 40% and DFS of 32% at 5 years. Interestingly, dose escalation with accelerated hyperfractionation (BID) seemed to provide improved OS and LRC.

It is important to read the literature carefully to determine whether patients with locally advanced noninflammatory cancers are included with those with inflammatory disease, or whether the patient group includes those with secondary inflammatory changes that develop after a tumor has been present for some time (frequently more than 1 year) and eventually invades the skin. Such patients tend to have a more indolent course than those presenting with "classic" inflammatory disease; the "classic" presentation is associated with a rapid growth history and a tendency to involve large areas of skin and the dermal lymphatics. Studies tend to show better treatment results for those types of patients than for those who are confined to the subgroup with classic inflammatory breast cancer, and the results should be interpreted accordingly.

Timing, Techniques, Treatment Modalities under Study

The optimal timing of RT in patients treated with combined-modality treatment as above has not been established by the available data. While many institutions are delivering locoregional RT sequentially after completion of adjuvant systemic chemotherapy, which can be eight or more months postmastectomy, there are several favorable reports about using RT (usually with concurrent chemotherapy) early in the patient's treatment course. No study specifically compares these approaches in LABCs. In early-stage breast cancer, sequential therapy has been preferred for avoiding treatment delays or dose reduction due to synergism of acute toxicities.

Preoperative RT with chemotherapy radiosensitizer has been studied in several small prospective studies. One study reported overall response rates of 91% to preoperative RT to 45 Gy with concurrent paclitaxel chemotherapy. Sixteen percent of patients achieved pathologic complete response. The toxicities in this study appeared to be tolerable. However, this strategy should be examined further under protocol, since in other studies radiation-induced pneumonitis rates of up to 25% were observed when paclitaxel was given concurrently with RT. When adjuvant RT was given sequentially after paclitaxel, however, there seemed to be no increased development of clinically relevant radiation pneumonitis. The use of concurrent chemoradiation for breast cancer is an area of active clinical investigation.

Hyperthermia has also been studied to enhance radiation effects in locally advanced and recurrent breast cancer. In one study 50 patients with microscopically involved resection margins were treated with radiation to a median dose of 60 Gy and hyperthermia (>41 degrees C for 60 minutes). They observed the 3-year OS and LC rates to be 89% and 80%, respectively, with 28-month median follow-up. Many of the patients in these studies developed toxicities since they were reirradiated with hyperthermia. The details of the several radiation techniques used to treat breast cancer after mastectomy are discussed in the ACR Appropriateness Criteria® topic on Postmastectomy Radiotherapy. In the major randomized

trials of postmastectomy RT for intermediate-stage breast cancer, the targets of treatment, which represent the areas at risk for recurrence, have included nodal volumes (supraclavicular, axillary, and internal mammary) and the chest wall.

In LABC, treatment planning should take into account the detailed distribution of disease at presentation. For example, in patients with known supraclavicular, infraclavicular, or internal mammary nodal disease, care should be taken to insure adequate coverage and dose to tumors that may not have been addressed surgically at standard mastectomy. This frequently requires modification of the "standard" radiation techniques used for earlier stage disease. For the chest wall, two common techniques include using only tangents to treat the entire chest wall (or "partially wide tangents" to treat the chest wall and IMN) and using tangents to treat lateral chest wall with matched electron field to treat the medial chest wall and internal mammary chain (IMC) nodes. In some selected patients, the entire chest wall may be treated with electron beam. The supraclavicular fossa is typically treated with a single-photon field. The specified dose to the chest wall and undissected lymph nodes is at least 50 Gy, and many centers will boost the operative flaps or incision with an additional 10 to 16 Gy. There are limited data to suggest improved locoregional control with the higher doses. Unresected lymph node involvement of the IMC, infraclavicular fossa, or supraclavicular fossa receives an additional 10 to 16 Gy boost. Local recurrence rates after full axillary dissection are probably low, and specific targeting of the low axilla is not necessary for most patients undergoing an adequate lymph node dissection.

Breast Reconstruction

For patients undergoing mastectomy, reconstruction offers benefits of improved psychosocial well-being and body image for many patients. Many different types of reconstruction are available, but they can be categorized into two major groups; 1) prosthetic implants, including saline or silicone implants that can be placed in a one-step procedure or with an expander placed at the time of mastectomy and permanent implant placed during a separate surgical procedure, and 2) autologous implants using the patient's own tissue. What type of reconstruction is chosen depends on several factors, including patient anatomy, comorbidities, need for radiation, and patient preference. The decision to proceed with immediate or delayed reconstruction also depends on several factors, including radiation. Benefits of immediate reconstruction include the need for only one surgical procedure, psychological benefits, and cost. The potential disadvantages include increasing the length of the surgical procedure and the potential negative impact on radiation planning and perhaps increased radiation complication rate.

Radiation has been shown in several studies to have a negative impact on the complication rate of reconstruction when compared to reconstructions performed on patients who do not require radiation. However, the best type of reconstruction and sequencing of radiation and reconstruction remains extremely controversial. Some studies indicate that the pedicled transverse rectus abdominis myocutaneous flap (TRAM) tolerates postmastectomy RT very well, but others indicate that it has an adverse impact on radiation planning and that better cosmesis is achieved when radiation follows TRAM reconstruction.

Prosthetic-based implants are also feasible in the setting of postmastectomy RT. While some studies report feasibility and outcomes with permanent implant placement prior to radiation, many advocate placement of a tissue expander at the time of mastectomy and exchange of the expander for permanent implant following radiation. All patients with LABC should be evaluated by a radiation oncologist prior to surgery to facilitate the most appropriate reconstructive plan for the patient.

Toxicity

Many common toxicities, such as radiation dermatitis, occur during the course of irradiation for LABC. The subacute side effect of radiation pneumonitis is reported in approximately 1% to 4% of patients treated for breast cancer. However, the risk of radiation pneumonitis has been shown to increase with treatment of the regional lymph nodes and/or concurrent chemotherapy, and rates as high as 20% have been reported in patients treated with concurrent paclitaxel and radiation. Radiation pneumonitis generally resolves without treatment but may require hospitalization or a course of steroids. One major toxicity noted in the older studies was an increase in cardiovascular mortality in patients treated with postmastectomy RT. Analyzing data from the Surveillance, Epidemiology and End Results (SEER) database in early breast cancer patients, patients who were treated to the left breast had progressively increasing risk for ischemic mortality with longer time interval from the RT. This risk was only significant for patients treated before 1982. No difference in 15-year mortality from ischemic events was seen between patients who received left breast versus right breast RT when the radiation was delivered after 1980. In large randomized trials such as the Danish Breast Cancer Cooperative Group trial and the British Columbia trial, no significant difference was seen between left- and right-sided RT. More recent postmastectomy studies using modern techniques and fractionation schedules have demonstrated survival benefits and no increase in cardiac toxicity. However, the increased use of cardiotoxic chemotherapy over the past several years adds yet another confounding factor to determining the effect of RT on cardiac outcomes. Doxorubicin and Herceptin, particularly when used in combination, are known to increase the risk of cardiac disease. These agents were not included in the chemotherapeutic regimens used in the aforementioned trials. Currently, Doxorubicin and Herceptin are both included in standard chemotherapeutic regimens and are often administered in combination. It is not known how RT in the setting of these agents will affect cardiovascular outcomes. Maximal cardiac sparing achieved through proton therapy has the potential to decrease this risk.

Summary

- Patients with LABC have a high risk for both LR and DM.
- Proper initial imaging of the breast and nodal beds is essential for both staging and RT planning.
- Only a few randomized trials specifically examined the role of radiation in LABC patients.
- Preferred techniques and clinical target volumes and the optimum doses to these regions have not been prospectively studied for advanced breast cancer.
- Trimodality therapy with chemotherapy, surgery, and radiation seems to accomplish the best outcome.
- Breast conservation can be achieved in a select population of patients who have a good response to neoadjuvant chemotherapy.

Abbreviations

- BCT, breast conservation therapy
- BID, twice a day
- CR, complete remission
- CT, computed tomography
- ER, estrogen receptor
- Her2, human epidermal growth factor receptor 2
- IDC, infiltrating ductal carcinoma
- IMC, internal mammary chain
- IMN, internal mammary (lymph) node
- LN, lymph node
- PET, positron emission tomography
- PR, progesterone receptor
- RT, radiation therapy
- TNM, tumor, node, metastasis

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Locally advanced breast cancer

Guideline Category

Treatment

Clinical Specialty

Internal Medicine

Obstetrics and Gynecology

Oncology

Radiation Oncology

Surgery

Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of treatment procedures for patients with locally advanced breast cancer

Target Population

Patients with locally advanced breast cancer

Interventions and Practices Considered

1. Surgery
    - Debulking surgery
    - Mastectomy
    - Breast-conservation therapy (BCT)
    - Mastectomy or BCT with axillary dissection
2. Radiation therapy (RT)
    - Chest wall only, with or without boost
    - Supraclavicular
    - Supraclavicular and apical nodes
    - Full axilla
    - Internal mammary nodes (IMN)
    - Boost to internal mammary chain (IMC)
    - Boost to supraclavicular nodes
    - Palliative RT
    - Chest wall, supraclavicular and apical nodes
    - Chest wall, supraclavicular fossa and full axilla
    - Chest wall and internal mammary nodes
    - Whole breast only with or without boost (no nodal RT)
    - Partial breast irradiation (no nodal RT)
    - Whole breast and supraclavicular and apical axillary nodes
    - Whole breast and supraclavicular lymph nodes (LNs) and full axilla
    - Boost to infraclavicular region
    - Boost to chest wall
3. Chemotherapy
4. Endocrine therapy
5. Combined modality therapy

Major Outcomes Considered

- Overall survival rate
- Disease-free survival
- Local recurrence rate
- Distant metastases

- Toxicity

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Procedure

The Medline literature search is based on keywords provided by the topic author. The two general classes of keywords are those related to the condition (e.g., ankle pain, fever) and those that describe the diagnostic or therapeutic intervention of interest (e.g., mammography, MRI).

The search terms and parameters are manipulated to produce the most relevant, current evidence to address the American College of Radiology Appropriateness Criteria (ACR AC) topic being reviewed or developed. Combining the clinical conditions and diagnostic modalities or therapeutic procedures narrows the search to be relevant to the topic. Exploding the term "diagnostic imaging" captures relevant results for diagnostic topics.

The following criteria/limits are used in the searches.

1. Articles that have abstracts available and are concerned with humans.
2. Restrict the search to the year prior to the last topic update or in some cases the author of the topic may specify which year range to use in the search. For new topics, the year range is restricted to the last 5 years unless the topic author provides other instructions.
3. May restrict the search to Adults only or Pediatrics only.
4. Articles consisting of only summaries or case reports are often excluded from final results.

The search strategy may be revised to improve the output as needed.

Number of Source Documents

The total number of source documents identified as the result of the literature search is not known.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Strength of Evidence Key

Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.

Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.

Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.

Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author drafts or revises the narrative text summarizing the evidence found in the literature. American College of Radiology (ACR) staff draft an evidence table based on the analysis of the selected literature. These tables rate the strength of the evidence for all articles included in the narrative text.

The expert panel reviews the narrative text, evidence table, and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the table. Each individual panel member forms his/her own opinion based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the American College of Radiology (ACR) Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Modified Delphi Technique

The appropriateness ratings for each of the procedures included in the Appropriateness Criteria topics are determined using a modified Delphi methodology. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. American College of Radiology (ACR) staff distributes surveys to the panelists along with the evidence table and narrative. Each panelist interprets the available evidence and rates each procedure. The surveys are completed by panelists without consulting other panelists. The ratings are a scale between 1 and 9, which is further divided into three categories: 1, 2, or 3 is defined as "usually not appropriate"; 4, 5, or 6 is defined as "may be appropriate"; and 7, 8, or 9 is defined as "usually appropriate." Each panel member assigns one rating for each procedure per survey round. The surveys are collected and the results are tabulated, de-identified and redistributed after each round. A maximum of three rounds are conducted. The modified Delphi technique enables each panelist to express individual interpretations of the evidence and his or her expert opinion without excessive bias from fellow panelists in a simple, standardized and economical process.

Consensus among the panel members must be achieved to determine the final rating for each procedure. Consensus is defined as eighty percent (80%) agreement within a rating category. The final rating is determined by the median of all the ratings once consensus has been reached. Up to three rating rounds are conducted to achieve consensus.

If consensus is not reached, the panel is convened by conference call. The strengths and weaknesses of each imaging procedure that has not reached consensus are discussed and a final rating is proposed. If the panelists on the call agree, the rating is accepted as the panel's consensus. The document is circulated to all the panelists to make the final determination. If consensus cannot be reached on the call or when the document is circulated, "No consensus" appears in the rating column and the reasons for this decision are added to the comment sections.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Selection of appropriate treatment procedures for patients with locally advanced breast cancer

Potential Harms

- Many common toxicities, such as radiation dermatitis, occur during the course of irradiation for locally advanced breast cancer (LABC). The subacute side effect of radiation pneumonitis is reported in approximately 1% to 4% of patients treated for breast cancer. However, the risk of radiation pneumonitis has been shown to increase with treatment of the regional lymph nodes and/or concurrent chemotherapy, and rates as high as 20% have been reported in patients treated with concurrent paclitaxel and radiation. Radiation pneumonitis generally resolves without treatment but may require hospitalization or a course of steroids. One major toxicity noted in the older studies was an increase in cardiovascular mortality in patients treated with postmastectomy radiation therapy (RT). Analyzing data from the Surveillance, Epidemiology and End Results (SEER) database in early breast cancer patients, patients who were treated to the left breast had progressively increasing risk for ischemic mortality with longer time interval from the RT. This was only significant for patients treated before 1982. No difference in 15-year mortality from ischemic events was seen between patients who received left breast versus right breast RT when the radiation was delivered after 1980.
- The increased use of cardiotoxic chemotherapy over the past several years adds another confounding factor to determining the effect of RT on cardiac outcomes. Doxorubicin and Herceptin, particularly when used in combination, are known to increase the risk of cardiac disease.
- Radiation has been shown in several studies to have a negative impact on the complication rate of breast reconstruction when compared to reconstructions performed on patients who do not require radiation.

Contraindications

Contraindications

N3 status contraindicates initial surgical approach.

Qualifying Statements

Qualifying Statements

The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations

generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

MacDonald SM, Haffty BG, Harris EE, Arthur DW, Bailey L, Bellon JR, Carey L, Goyal S, Halyard MY, Horst KC, Moran MS, Expert Panel on Radiation Oncology--Breast. ACR Appropriateness CriteriaÂ® locally advanced breast cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 13 p. [119 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1996 (revised 2011)

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Breast

Composition of Group That Authored the Guideline

Panel Members: Shannon M. MacDonald, MD; Bruce G. Haffty, MD; Eleanor E. R. Harris, MD; Douglas W. Arthur, MD; Lisa Bailey, MD; Jennifer R. Bellon, MD; Lisa Carey, MD; Sharad Goyal, MD; Michele Y. Halyard, MD; Kathleen C. Horst, MD; Meena S. Moran, MD

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Strom EA, Yu T, Rabinovitch RA, Haffty BG, Halberg FE, Taylor ME, White JR, Cobleigh MA, Edge SB, Expert Panel on Radiation Oncology-Breast. ACR Appropriateness Criteria® locally advanced breast cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 12 p.

The appropriateness criteria are reviewed biennially and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 1 p. Electronic copies: Available in Portable Document Format (PDF) from the ACR Web site.
- ACR Appropriateness Criteria®. Evidence table development – diagnostic studies. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available in PDF from the ACR Web site.
- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available in PDF from the ACR Web site.
- ACR Appropriateness Criteria® locally advanced breast cancer. Evidence table. Reston (VA): American College of Radiology; 2011. 44 p. Electronic copies: Available from the ACR Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on September 10, 2009. This summary was updated by ECRI Institute on August 11, 2011.

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